recommended for immediate passive immunization against tetanus as an emergency measure in persons sustaining other than clean minor wounds when immunization history is uncertain or when less than 2 doses of tetanus toxoid have been administered. When the wound is more than 24 hours old, however, the product should be given to patients who have received 2 doses of tetanus toxoid.

Tetanus immune globulin (human) is preferred over the similar product of equine or bovine origin.

The usual dosage for adults and children is 250 units regardless of body weight, although for children a dosage of 4 units per kg body weight may be adequate but larger doses are not harmful. The approximate volume necessary to supply the recommended dosage is not given; the material is supplied in a syringe.

Large doses (usually 3,000 to 6,000 units) of tetanus immune globulin (human) have been used therapeutically for treatment of clinical tetanus.

The use of combined active and passive immunization is discussed. If tetanus toxoid is not given immediately, active immunization with tetanus toxoid should be completed in all cases, either immediately or shortly after treatment.

b. *Contraindications.* None are stated, but it is mentioned under adverse reactions that reactions following intramuscular injections are infrequent and usually confined to the area of injection. Sensitization to repeated injections of tetanus immune globulin is said to be extremely unusual. As a precaution, the product should be administered intramuscularly, and not intravenously.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The submission to the Panel (Ref. 12) includes referral to the pertinent literature only. This specific product appears not to have been evaluated in any form in humans.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No adverse experiences have been reported in a 5-year span between 1969 and 1974 from the use of hundreds of thousands of doses distributed worldwide. The company has received 61 complaints in 51 reports. The tetanus immune globulin was cloudy in five of these cases, the remaining reports related to packaging defects.

c. *Benefit/risk ratio.* Assuming the product is effective as discussed in the Generic Statement, the benefit-to-risk assessment should be satisfactory.

4. *Critique.* The selection and monitoring of donors is not described, neither is the method of obtaining informed consent described. Labeling is generally satisfactory, except that the approximate volume of the dose should be stated. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Travenol Laboratories, Inc., Hyland Division

1. *Description.* Tetanus immune globulin (human), as produced by Travenol Laboratories, is a sterile 15 to 18 percent solution of immuno-globulin fraction of the plasma of persons who have been hyperimmunized with tetanus toxoid. The solution is made isotonic and stabilized with 0.3 molar glycine. It contains 0.1 percent sodium chloride and 0.01 percent thimerosal as a preservative. The globulin is precipitated by the alcohol fractionation technique of Cohn. It is packaged in 250-unit vials.

2. *Labeling*—a. *Recommended use/indications.* This product is said to be useful in the treatment of injured persons at risk of tetanus and who need the immediate protection offered by tetanus antitoxin. Since it is of human origin, it offers two advantages over an antitoxin of nonhuman (equine) origin: (1) the risk of immediate or delayed sensitivity reactions is practically nonexistent; (2) fewer antitoxin units are required to produce a longer lasting effect. The labeling is quite specific in terms of who should receive tetanus immune globulin, containing not only the specific recommendations of the Public Health Service Advisory Committee on Immunization Practices, but also a rather cogent discussion of the recommendations.

b. *Contraindications.* No absolute contraindications are listed. A precaution against intravenous administrative is included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data relative to the Travenol Laboratories' product are cited in the submission to the Panel (Ref. 13).

b. *Safety*—(1) *Animal.* This product meets Federal requirements

(2) *Human.* No specific data relative to this product are cited.

c. *benefit/risk ratio.* The benefit-to-risk assessment of this product appears to be satisfactory.

4. *Critique.* This submission, while brief, is quite to the point. Some specific details are provided relative to the testing for hepatitis B antigen, and to the hyperimmunization of donors. The information supplied by the manufacturer, the animal tests that the product is required to pass, and the general body of data regarding the safety and efficacy of tetanus immune globulin (human), as summarized in the Generic Statement on Tetanus Immune Globulin, are sufficient to place this product in Category I. For prophylactic use see Generic Statement.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Wyeth Laboratories, Inc.

1. *Description.* Tetanus immune globulin (human) is a sterile 16.5 (±1.5) percent solution of human immunoglobulin prepared by Cohn cold ethanol fractionation of plasma from donors hyperimmunized with tetanus toxoid. The final product contains 0.3 molar glycine as a diluent and stabilizer and 0.01 percent thimerosal as a preservative. This product was prepared from blood that was nonreactive when tested for hepatitis B antigen.

Wyeth Laboratories purchases from Cutter Laboratories sterile tetanus immune globulin in bulk volume that has been released by the Bureau of Biologics. The product is used in the TUBEX hypodermic syringe. The manufacturing procedure for the Cutter Laboratories' products, for which there is a separate application, thus applies also to the Wyeth Laboratories' product, and the reader is referred to the product review for the Cutter Laboratories' product. In summary, the Cutter Laboratories' manufacturing process appears satisfactory.

The Wyeth Laboratories' product is designed to contain not less than 175 antitoxin units per mL. The degree to which this minimal potency level is exceeded is a direct function of the degree of hyperimmunization reflected in the donor plasma pool.

2. *Labeling*—a. *Recommended use/indications.* Tetanus immune globulin (human) is indicated for passive immunization against tetanus in any person with an injury that might be contaminated with tetanus organisms, who has never been actively immunized with tetanus toxoid, or whose active immunity status is uncertain or of questionable validity and cannot be established. Passive immunization is probably also indicated for those

persons activily immunized with tetanus toxoid whose last recall (booster) dose or last dose of the basic immunizing series (reinforcing dose) was given more than 10 years prior to injury and if a delay of more than 24 hours has occurred between the time of injury and initiation of specific tetanus prophylaxis.

The need to initiate active immunization with tetanus toxoid adsorbed at the same time as the human immunoglobulin is clearly spelled out.

The recommended adult dose is 250 units intramuscularly. The dose for children may be calculated on the basis of body weight (4.0 units per kg) or the entire contents of the TUBEX may be injected regardless of body weight since theoretically the same amount of toxin would be produced by infecting tetanus organisms regardless of whether the infection is occurring in an adult or child.

The half-life of tetanus immune globulin is approximately 4 weeks. In situations where the threat of tetanus persists or for treatment of the disease, repeated doses may be administered.

b. *Contraindications.* None is specifically mentioned, but local and systemic reactions are said to be infrequent and usually mild. The risk of isoimmunization is ever present when immunoglobulin is administered to immunologically competent persons. Under precautions, it is warned that the product should not be given intravenously, because severe pyrogenic and fatal cardiovascular reactions have occurred following intravenous administrations. Tests for sensitivity should not be done.

3. *Analysis.* No specific analysis of efficacy or safety is outlined in this submission (Ref. 14). However, the product is purchased from Cutter Laboratories, for which a detailed separate submission is available. The reader is referred to the analysis of this product. Date on efficacy, based on studies of antitoxin in humans after administration of this product, are available. No field trials have been carried out, neither would such an undertaking be feasible at the present time. No data from the complaint file are available.

a. *Benefit/risk ratio.* Since the product produces satisfactory levels of antitoxin in human subjects with originally low antitoxin levels, and the product appears to be safe, the benefit-to-risk assessment should be satisfactory.

4. *Critique.* The efficacy and safety of this product is the same as for the Cutter Laboratories' product. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

References

(1) BER Volume 2108.
(2) BER Volume 2039.
(3) BER Volume 2071.
(4) BER Volume 2025.
(5) BER Volume 2087.
(6) "A Guide to Prophylaxis Against Tetanus in Wound Management," American College of Surgeons, 1972 Revision, pp. 32–33, December 1972.
(7) Heurich, A.E., J.C.M. Brust, and R.W. Richter, "Management of Urban Tetanus," *Medical Clinics of North America,* 57(6):1373–1381, 1973.
(8) BER Volume 2030.
(9) BER Volume 2055.
(10) BER Volume 2012.
(11) BER Volume 2115.
(12) BER Volume 2004.
(13) BER Volume 2107.
(14) BER Volume 2018.

MISCELLANEOUS PRODUCTS

Collagenase Manufactured by Advance Biofactures Corporation, Distributed by Knoll Pharmaceutical Corporation

1. *Description.* Collagenase ABC ointment and collagenase santyl ointment contains the enzyme collagenase extracted from cultures of *Clostridium histolyticum* suspended in a petrolatum base in a concentration of 250 units per gram. Collagenase is an enzyme which digests undenatured collagen fibers. Collagen is produced by fibroblasts and exists in the form of an interwoven fiber consisting of three strands which in turn are made up of a left-handed poly-1-proline type helix. The ropelike coiled structure then has an opposite (right handed) supertwist. The uniqueness of collagenases compared with other proteolytic enzymes is that they attack the intact helical structure of collagen. Although collagenase from other sources are described, only that from *Clostridium histolyticum* has been produced in significant amounts for therapeutic application.

Other proteolytic enzymes employed in debridement act on fibrin and on denatured collagen but do not break up native collagen fibers which anchor the eschars of large ulcers, particularly burns, to the wound.

Collagenase is prepared from the supernatant of broth cultures of a standard strain of *Clostridium histolyticum.* The enzyme is concentrated by ammonium sulphate precipitation and the concentrate is sterilized by x-radiation. It is mixed with white petrolatum U.S.P. and distributed in containers without preservatives. The potency of the enzyme is measured by an assay involving the digestion of bovine Achilles tendon and the subsequent measurement of liberated amino acids with ninhydrin reagent.

2. *Labeling*—a. *Recommended use/indications.* The ointment is recommended as a therapeutic debriding agent for dermal ulcers and burns and particularly to remove dense eschars which anchor necrotic tissue to the base of wounds and delay their epithelization. The enzyme is active at physiologic pH and temperature and loses activity rapidly at unfavorable conditions. The activity is also adversely affected by detergents, hexachlorophene, and heavy metals such as mercury and silver which are contained in certain antiseptic solutions (e.g., Burow's Solution). Lesions must be thoroughly washed with normal saline before applying collagenase. The ointment should be confined to the lesions and normal surrounding skin should be protected by dressings. Concurrent infection should be treated with topical antibiotics. Debilitated patients must be closely observed for the theoretical possibility of disseminated infection and bacteremia during the debridement. Crosshatching a thick eschar with a scalpel to increase penetration of the enzyme is helpful as is removing and loosening as much necrotic tissue as possible with forcepts and scissors. Excess ointment should be removed with each daily change of dressing. It is appropriately pointed out that treatment of necrotic lesions other than dermal ulcers and severly burned areas has been limited only to reports of clinical observations without controls.

b. *Contraindications.* Since the enzyme is a protein, sensitization may develop with prolonged use although none has been reported. Adverse reactions have not been noted when used as recommended.

3. *Analysis*—a. *Efficacy.* Five contolled and 12 partially controlled studies are cited in the submission to the Panel (Ref. 1) as supporting evidence of efficacy. The five controlled studies were double-blind and included placebos. The controlled studies involved a total of 79 patients with dermal ulcers or decubiti. Some of these studies employed inactivated enzyme as placebo, were randomized, and a relatively brief treatment period was evaluated to prevent obvious changes in the wounds from unblinding the study. Attempts were made to score the responses objectively by recording

wound size, using serial photographs, obtaining cultures, and recording estimates of the amount and character of pus, debris, odor, and inflammation. In all controlled studies there was a statistically significant difference in favor of collagenase over placebos in all measured parameters of wound healing (Table 1).

b. *Safety.* This product is well tolerated when used properly and no significant untoward effects have been reported except occasional erythema. Animal studies reveal a high level of tolerance and low toxicity in rabbits, mice, and guinea pigs by injection of enzyme powder subcutaneously, intramuscularly, and intravenously. Topical application in animals produces local erythema but no systemic toxicity. This product meets Federal requirements.

TABLE 1.—SUMMARY TABLE-EFFICACY

Number and investigator	Exhibit No.	Diagnosis	Patients treated	Lesions treated [2]	Satisfactory Response [3] E or G
1—Controlled studies:					
Varma				C-10	9
	34	Dermal ulcers; decubiti	20	P-10	1
German				C-32	31
	13	Decubiti	34	P+-22	5
Bardfeld				C-9	9
	2	Lower extremity ulcers	8	P+-5	0
Ambrus				C-17	11
	1	Decubiti	10	P-10	0
Boxer		Venous or arterial ulcers; decubiti		C-10	9
	7 and 8	dedubiti	7	P-7	1
2—Partially controlled and uncontrolled studies:					
German				C-15	12
	13	Decubiti	26	P-11	1
Boxer	7 and 8	P. V. ulcers and decubiti	40	C-62	58
Georgiev	12	Decubiti	21	C-21	17
Rein	31	Burns	6		6
Barrett				C-12	12
	3	Decubiti	12	P-4	0
Original submission				C-327	270
	33	Dermal ulcers, burns	268	P+-155	70
Lippmann	20	Dermal ulcers	40	C-40	34
Maxurek	24	Dermal ulcers, wounds; burns [4]	1,356	C-1,356	1,085
Zimmermann	37	Dermal ulcers	64	C-64	Not reported
Zimmermann	36	Burns	230	C-230	Not reported
Mahler	22	Extensive burns	59	C-59	Not reported
Blum	5	Dermal ulcers, decubiti; burns	71	C-71	59 Fair—Good

[1] Refers to Exhibit in manufacturer's submission to the Panel (Ref. 1).
[2] C=Collagenase, P=Placebo, P+=Controls consisted of either placebo or other active agents.
[3] E=Excellent, G=Good.
[4] Includes Zimmermann studies.

c. *Benefit/risk ratio.* For use in the treatment of dermal ulcers and burns, the ratio is satisfactory since the risk is small and with proper usage there is often significant improvement in the character of the wound without interference with antibiotic efficacy or other forms of treatment.

4. *Critique.* There is little question that this enzyme can digest intact collagen and that in large, eschared dermal ulcers described, such as those encountered in decubiti and burns, surface debridement can be enhanced, and that decrease in pus, inflammation, and odor is quite regularly observed; adverse reactions are few. The labeling is accurate and pertinent and clearly defines the limitations of the product and instructions for its use. It is not clear, however, why, in some labels, routine topical antibiotic treatment is insisted upon rather than advised when indicated by the degree of infection. Labeling for these products may have to be revised to discuss the possible interference of silver sulfadiazine or sulfamylon with the enzymatic activity of collagenase, an issue not fully resolved by the Fox, Sanford, and Sampath paper (Ref. 2).

5. *Recommendations.* The Panel recommends that these products be placed in Category I and that the appropriate license(s) be continued because there is satisfactory evidence of safety and effectiveness for the products when used as recommended, provided the labeling is revised in accordance with this Report.

References

(1) BER Volume 2119 and 2120.
(2) BER Volume 2118.

Bibliography

(1) Bardfeld, L. A., "Treatment of Dermal Ulcers of the Lower Extremity With Collagenase," *in* "Collagenase," Mandel, I. (editor), New York, Gordon and Beach, pp. 191–195, 1972.

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Generic Statement

Streptokinase-Streptodornase

Streptokinase-Streptodornase is a mixture of extracellular enzyme activators and enzymes produced by some sero-groups of hemolytic streptococci. These agents liquify fibrin and nucleoproteins in purulent exudates. Streptokinase effects the conversion of plasminogen to plasmin, a proteolytic plasma enzyme. The latter digests fibrinogen and fibrin, resulting in fibrinolysis. Streptodornase is a group of enzymes that act in stages to liquify deoxyribonucleoprotein, the viscous cellular protein present in pus.

Tillett and Garner first described the fibrinolytic activity of hemolytic streptococci in 1933. By 1949 partial purification of the streptococcal extracellular enzymes that liquify pus was accomplished and the liquid

preparation of Streptokinase-Streptodornase was introduced into therapy by Tillett and Sherry who instilled it into the pleural cavity to accomplish lysis of thick exudates. Topical use of the preparation for "enzymatic debridement" of purulent exudates was widely employed by 1950 and by 1955 intramuscular injections were tried for the nonspecific suppression of inflammation and edema in certain local infections. In 1958, buccal administration of tablets was introduced as an alternative to intramuscular injections and by 1960 clinical investigation of the effectiveness of oral tablets began, followed by marketing in 1963.

Production

The mixture of Streptokinase-Streptodornase employed in topical therapy is an extracellular product of a Group C strain of streptococcus grown for about 18 hours in a medium consisting of acid-hydrolyzed casein fortified with sugar, minerals, vitamins, and a reducing substance. The culture filtrate is purified by the method of cold alcohol fractionation. A unit of streptokinase is the quantity required to produce from plasminogen an amount of plasmin sufficient to dissolve a standard fibrin clot in 10 minutes at 35 °C. A unit of streptodornase is the quantity necessary to cause a decrease of 1 viscosity unit in 10 minutes at 30 °C in a reaction mixture of 2.4 mL of deoxyribonucleic acid of a standard relative viscosity. The streptokinase-streptodornase mixture also includes a number of other streptococcal extracellular enzymes such as deoxyribonuclease, hyaluronidase, nucleotidase, and nucleosidase, all of which may contribute to the liquifying effect of the product on purulent exudates. The mixture is apparently free of streptolysin and proteinase. The solution is buffered with phosphate. Some preparations are mixed with carboxymethylcellulose 4.5 percent jelly. Mixtures are unstable at room temperature but retain full potency for 2 weeks when refrigerated at 2 to 10 °C.

Labeling

1. *Use and indications.* Compatibility with antibiotics is not yet clearly determined and it is recommended that antibiotics be administered separately. Streptokinase and streptodornase administered in solution either locally or parenterally are both antigenic and frequently elicit antienzyme antibodies. These antienzymes, antistreptokinase and antistreptococcal DNAses may also appear after hemolytic streptococcal infections. A high titer is not harmful but requires increasing dosage of streptokinase-streptodornase to exert an effect. No antigenic responses have been reported for the buccal or oral forms but it is likely that they may also occur.

The rationale for topical or local administration of streptokinase-streptodornase is the augmentation of liquefaction of fibrin and pus where such action is considered desirable to produce healing more rapidly and to prevent extensive adhesions and fibrosis. The product does not act upon mucoproteins, fibroblasts, fibrous tissues, or collagen in vivo although lysis in vitro has occasionally been reported.

Streptokinase is considered the most effective therapeutic agent available for enhancing the resolution of fibrin in closed body cavities containing inflammatory effusions (or clotted blood). It is superior to proteolytic enzymes for this purpose. Most inflammatory exudates contain plasminogen and the mechanism of fibrinolysis results from the diffusion of the plasminogen activator into the fibrinous substance resulting in production of plasmin within the fibrin network and thus rapid fibrinolysis. In addition, streptokinase is inactivated slowly (except by antistreptokinase) in contrast to proteolytic enzymes. On surface wounds, however, where proteolytic enzymes such as trypsin are not blocked by tissue inhibitors, plasmin is not as effective as other more widely active proteolytic enzymes. Thus, third degree burn eschars and necrotic connective tissues are not susceptible to plasmin digestion but are attacked by trypsin.

Except for the occasional presence of antistreptodornase, inflammatory exudates contain little which inhibits the activity of topically administered streptodornase. When streptodornase is administered systemically, however, its inactivation is rapid. For this reason, parenterally administered streptokinase-streptodornase owes whatever specific effect it may have exclusively to streptokinase.

A peculiar situation exists, therefore, whereby streptokinase-streptodornase has been licensed for parenteral as well as topical use although any claim for parenteral efficacy would have to be unrelated to the action of streptodornase. Moreover, purified streptokinase for intravenous use in the treatment of thromboembolism is now available commercially and two preparations have recently been licensed.

The administration of streptokinase-streptodornase intramuscularly in dosages of 5,000 units of streptokinase twice daily has been recommended in the treatment of edema associated with infection and trauma, particularly cellulitis and thrombophlebitis, rather than extensive tissue necrosis. Claims have been made for rapid reduction in inflammatory reactions within a few days of initiation of treatment. About 10 percent of treated patients develop fever thought to be attributable to streptokinase-streptodornase. The recommended doses do not produce fibrinolysis, hematomas, petechiae, or hemmorrhage.

Package inserts recommend that streptokinase-streptodornase intramuscularly be accompanied by the systemic administration of a broad spectrum antibiotic agent. It is also emphasized that in the treatment of abscesses, streptokinase-streptodornase, intramuscularly, may reduce accompanying cellulitis but should not replace sound surgical principles of drainage.

Administration (as recommended by current labeling). Streptokinase-streptodornase has been tried and recommended by the manufacturer for a long list of clinical applications. Appraisal of these is complicated and compounded by distinctions between topical application, local instillation into body cavities and abscesses, intramuscular administration, buccal tablets for parenteral administration, and oral tablets.

Topical administration may be achieved in a variety of ways including dressing with streptokinase-streptodornase solutions, or application of streptokinase-streptodornase in a carboxymethylcellulose jelly. Instillation and irrigation in body cavities are effected by repeated applications and drainage as exudates are thinned.

Intramuscular streptokinase-streptodornase is recommended by the manufacturers for treatment of inflammation in inaccessible areas. It is suggested that such intramuscular injections deep into the gluteal muscle induce a "fibrinolytic response in areas of inflammation of any site." This is alleged to result in rapid reversal of the inflammatory process presumably by the digestion of fibrin in the edema fluid and reduction of the viscosity of the fluid.

Buccal tablets are recommended to produce results comparable to intramuscular administration. The tablets are placed in the buccal pouch or under the tongue and allowed to dissolve slowly for 10 minutes or more.

Oral administration is also advised on the grounds that gastric juice contains a

considerable amount of "plasminogen proactivator," which reacts with streptokinase, and the product is supposedly absorbed without inactivation.

Clinical applications suggested by manufacturers include: treatment of abscesses (by topical application only—parenteral has not been considered effective), bronchopulmonary inflammation by aerosol or instillation, or by systemic administration; cellulitis, ulceration, and necrosis; gangrene from occlusive arterial disease (excluding dry gangrene); radiation necrosis; cervicitis; contusions, ecchymoses, and hematomas (topical, intramuscular, and oral); cystitis, bladder clots, ureteral calculi (all forms of administration); dental and oral disorders, dermatological conditions (e.g., cystic acne vulgaris); empyema and hemothorax; nontuberculous purulent meningitis; suppurative joint infections; osteomyelitis; pericarditis; ophthalmic inflammation; puerperal pelvic conditions; pulmonary hyaline membrane syndrome; sinusitis and many other inflammatory conditions.

Thrombophlebitis and thromboembolic disease require special comment. Purified products of streptokinase are now licensed for intravenous and intraarterial therapy. Several cooperative trials have been conducted on the effectiveness of intravenous urokinase and streptokinase in pulmonary embolism and deep vein thrombosis and in myocardial infarction and other forms of arterial thrombosis. These and other studies have been summarized in several excellent recent reviews.

2. *Contraindications and precautions recommended in current labeling*—a. *Topical and local use.* Should be used only in areas where adequate drainage is maintained or in closed spaces, such as the pleural cavity when adequate drainage or operation is possible. A local increase of exudation and leukocytosis occurs in the first 24 hours. Pyrogenic reactions are the most common untoward effect. Allergic reactions are rare but the physician should be alert to the possibility of such reactions. Streptokinase-streptodornase is antigenic, which limits the effectiveness of prolonged and repeated use.

b. *Intramuscular use.* Administration of broad spectrum antibiotics is advised concomitantly with the use of streptokinase-streptodornase intramuscularly. Appropriate surgical drainage is also urged. Defects in blood coagulation of liver disease are contraindications to parenteral use.

c. *Buccal tablets.* Buccal tablets are contraindicated in patients with reduced plasminogen or fibrinogen. Urticaria and rashes have been reported.

d. *Oral tablets.* Oral tablets are also contraindicated in patients with reduced plasminogen and fibrinogen.

Safety

No reactions have been reported from 1969 through April 1974 for the use of topical streptokinase-streptodornase produced by Lederle Laboratories.

Efficacy

To clarify considerations of safety and efficacy, the recommended uses of streptokinase-streptodornase should be clearly separated into three general categories: (i) Debridement, (ii) anti-inflammation, and (iii) thrombolysis; and the effectiveness of each product should be considered in relation to these categories. (See Table 1.)

1. *Debridement.* On theoretical grounds, by in vitro studies, and by clinical observations, topical and local use of streptokinase-streptodornase can be expected to liquefy pus and blood clots in vivo in several conditions and under appropriate methods of application. Topical and local use of streptokinase-streptodornase may have efficacy in some situations where enhanced liquefaction of pus and fibrin is beneficial and where the products of inflammation can be properly drained. Such uses are clearly only adjunctive to other medical and surgical procedures. The effectiveness of streptokinase-streptodornase can only be assessed, therefore, as a supportive rather than primary therapeutic agent. Furthermore, instruction for its usage must clearly define its major limitations as a topical agent—its substrates must be available and accessible and the enzymes and activators must be in continued contract with their substrates under physiological conditions of temperature and pH. For these reasons, instructions for the local and topical uses should be clearly subdivided into topographical categories, such as: (i) body cavities, (ii) wounds and fistulae, and (iii) the lumina of body passages (bronchi, urethra, external auditory canal, etc.). Extensive lists of clinical conditions for which streptokinase-streptodornase is recommended by the manufacturer do not offer critical guidance to the selection of the appropriate clinical indications.

Body cavities. Streptokinase-streptodornase may be effective in liquefying pus and fibrin in certain body cavities as in the case of treatment of the appropriate stages of empyema or hemothorax, provided that adequate drainage is maintained. Lysis of inflammatory products and the local irritative effect of streptokinase-streptodornase cause an increased volume of fluid to accumulate in a closed cavity and the ease with which a cavity can be drained should be considered before employing the product. The use of streptokinase-streptodornase intrathecally is not generally recommended for primary forms of meningitis because of the severe local reactions it produces. The irrigation of neurosurgical drainage systems in certain cases of chronic obstruction of the cerebrospinal circulation may not be contraindicated, however, but would depend upon well-informed clinical judgment as to its value. Instillation of streptokinase-streptodornase into body cavities probably offers the best opportunities to maintain local contact of the product with its substrates and yet it is not extensively employed in current practice because of other effective medical and surgical approaches to drainage of such cavities.

Wounds and fistulae. Topical therapy with streptokinase-streptodornase may also have adjunctive effectiveness in the treatment of wounds and fistulae by enhancing debridement, but the need for maintaining continuous contact with the surface of these lesions must be emphasized. Suspension of streptokinase-streptodornase in a jelly (such as carboxymethylcellulose) may facilitate such application, but again efficacy would depend upon the ingenuity with which would contact is maintained with either solutions or pastes. There seem not to be significant reactions or contraindications to such topical use.

Luminal applications. The same issues, discussed above, apply to the efficacy of debridement of such tracts as the bronchi, urethra, auditory canals, etc. The clinical investigative evidence for the effectiveness of streptokinase-streptodornase in the debridement of these areas is even more difficult to assess than debridgement of body cavities and wounds. So many variables are included in attempts to maintain good drainage of the respiratory, urinary, and other tracts, that the design of an effective investigative protocol to demonstrate clear adjunctive efficacy of streptokinase-streptodornase would be very difficult if not impossible. Some degree of efficacy could be assumed, however, if the recommendations for topical use are followed closely.

2. *Anti-inflammatory effects of streptokinase-streptodornase.* The evidence of the parenteral use of